

WHAT IS CLAIMED IS:

1. A method for directly delivering an immunomodulatory substance into an intradermal space within mammalian skin comprising administering the substance through at least one hollow needle having an outlet with an exposed height between 0 and 1 mm, said outlet being inserted into the skin to a depth of between 0.3 mm and 2 mm, such that delivery of the substance occurs at a depth between 0.3 mm and 2 mm.

2. The method according to claim 1 wherein the delivered substance has improved pharmacokinetics compared to pharmacokinetics after subcutaneous injection.

3. The method of claim 1 wherein the administration is through at least one small gauge hollow needle.

4. The method of claim 1 wherein the needle has an outlet with an exposed height between 0 and 1 mm.

5. The method of Claim 1 wherein injecting comprises inserting the needle to a depth which delivers the substance at least about 0.3 mm below the surface to no more than about 2 mm below the surface.

6. The method of Claim 1 wherein administering comprises inserting the needle into the skin to a depth of at least about 0.3 mm and no more than about 2 mm.

7. The method of claim 2 wherein the improved pharmacokinetics is increased bioavailability of the substance.

8. The method of claim 2 wherein the improved pharmacokinetics is a decrease in  $T_{\max}$ .

9. The method of claim 2 wherein the improved pharmacokinetics is an increase in  $C_{\max}$ .

10. The method of claim 2 wherein the improved pharmacokinetics is a decrease in  $T_{lag}$ .
11. The method of claim 2 wherein the improved pharmacokinetics is enhanced absorption rate.
12. The method of claim 1 wherein the substance is administered over a time period of not more than ten minutes.
13. The method of claim 1 wherein the substance is administered over a time period of greater than ten minutes.
14. The method of claim 1 wherein the substance is a protein or peptide.
15. The method of claim 1 wherein the substance is administered at a rate between 1 nL/min. and 200 mL/ min.
16. The method of claim 1 wherein said substance is an immunostimulant.
17. The method of claim 1 wherein said substance is an immunosuppressant.
18. The method of claim 1 wherein said substance is selected from the group consisting of an interferon, an interleukin, an anti-inflammatory agent, a tumor targeting compound, and a bacterial cell wall component or synthetic derivative thereof.
19. The method of claim 18 wherein said substance is a lipopolysacharride or BCG, or a synthetic derivative thereof.
20. The method of claim 18 wherein said substance is  $\alpha$  interferon.
21. The method of claim 1 wherein the needle(s) are inserted substantially perpendicularly to the skin.

22. A method of administering an immunomodulatory substance comprising injecting or infusing the substance intradermally through one or more microneedles having a length and outlet suitable for selectively delivering the substance into the dermis to obtain absorption of the substance in the dermis.

23. The method of Claim 22 wherein absorption of the substance in the dermis produces improved systemic pharmacokinetics compared to subcutaneous administration.

24. The method of Claim 23 wherein the improved pharmacokinetics is increased bioavailability.

25. The method of Claim 23 wherein the improved pharmacokinetics is decreased  $T_{\max}$ .

26. The method of claim 23 wherein the improved pharmacokinetics is an increase in  $C_{\max}$ .

27. The method of claim 23 wherein the improved pharmacokinetics is a decrease in  $T_{\text{lag}}$ .

28. The method of claim 23 wherein the improved pharmacokinetics is an enhanced absorption rate.

29. The method of claim 22 wherein the length of the microneedle is from about 0.5 mm to about 1.7 mm.

30. The method of Claim 22 wherein the microneedle is 30 gauge or narrower.

31. The method of Claim 22 wherein the microneedle has an outlet of from 0 to 1 mm.

32. The method of Claim 22 wherein the microneedle is configured in a delivery device which positions the microneedle perpendicular to skin surface.

33. The method of Claim 22 wherein the microneedle needle is contained in an array of microneedles needles.

34. The method of Claim 33 wherein the array comprises 3 microneedles.

35. The method of Claim 33 wherein the array comprises 6 microneedles.

36. The method of claim 22 wherein said substance is an immunostimulant.

37. The method of claim 22 wherein said substance is an immunosuppressant.

38. The method of claim 22 wherein said substance is selected from the group consisting of an interferon, an interleukin, an anti-inflammatory agent, a tumor targeting compound, and a bacterial cell wall component or synthetic derivative thereof.

38. The method of claim 38 wherein said substance is a lipopolysacharride or BCG, or a synthetic derivative thereof.

40. The method of claim 38 wherein said substance is  $\alpha$  interferon.

41. A method for delivering an immunomodulatory substance to a subject comprising : contacting the skin of the subject with a device having a dermal-access means for accurately targeting the dermal space of the subject with an efficacious amount of the bioactive substance.

42. The method of claim 41 wherein the pharmacokinetics of the immunomodulatory substance is improved relative to the pharmacokinetics of the substance when administered subcutaneously.

43. The method of claim 42 wherein the improved pharmacokinetics is an increase in bioavailability.

44. The method of claim 42 wherein the improved pharmacokinetics is a decrease in  $T_{\max}$ .

45. The method of claim 42 wherein the improved pharmacokinetics comprises an increase in  $C_{\max}$  of the substance compared to subcutaneous injection.

46. The method of claim 42 wherein the improved pharmacokinetics is a decrease in  $T_{\text{lag}}$ .

47. The method of claim 42 wherein the improved pharmacokinetics is an enhanced absorption rate.

48. The method of Claim 41 wherein the dermal access means comprises one or more hollow microcannula having a length of from about 0.3 to about 2 mm.

49. The method of Claim 41 wherein said dermal access means comprises one or more hollow microcannula having an outlet with an exposed height between 0 and 1 mm.

50. The method of Claim 41 wherein the substance is an immunostimulant.

51. The method of claim 41 wherein said substance is an immunosuppressant.

52. The method of claim 41 wherein said substance is selected from the group consisting of an interferon, an interleukin, an anti-inflammatory agent, a tumor targeting compound, and a bacterial cell wall component or synthetic derivative thereof.

53. The method of claim 52 wherein said substance is a lipopolysacharride or BCG, or a synthetic derivative thereof.

54. The method of claim 52 wherein the substance is  $\alpha$  interferon.

55. A method for delivering an immunomodulatory substance into tissue comprising delivering the substance within or beneath the skin at least into the intradermal space to access one or more compartments, which compartments afford the substance different pharmacokinetics, which enhance the effectiveness of the substance in terms of a resultant composite pharmacokinetics.

56. The method of claim 55 wherein the substance is delivered to a site which includes two or more of the compartments.

57. The method of claim 55 wherein the substance is delivered to multiple sites which each include one or more of the compartments.

58. The method of claim 55 wherein the delivery of the substance is by a needle or cannula.

59. The method of Claim 58 wherein a single needle is inserted into the intradermal space.

60. The method of Claim 58 wherein multiple needles or needle arrays are inserted into the intradermal space.

61. The method of Claim 60 wherein the multiple needles have different lengths.

62. The method of Claim 58 wherein the needle is about 300  $\mu\text{m}$  to about 5 mm long.

63. The method of Claim 62 wherein the needle is about 500  $\mu\text{m}$  to about 1 mm long.

64. The method of Claim 59 wherein the needle has an outlet placed at a depth of about 300  $\mu\text{m}$  to about 2 mm when the needle is inserted into the intradermal space.

65. The method of Claim 64 wherein the outlet is at a depth of about 500  $\mu\text{m}$  to about 1.7 mm when the needle is inserted.

65. The method of Claim 65 wherein the outlet is at a depth of about 750  $\mu\text{m}$  to about 1.5 mm when the needle is inserted.
66. The method of Claim 64 wherein the outlet has an exposed height of about 0 to about 1 mm.
67. The method of Claim 66 wherein the outlet has an exposed height of about 0 to about 300  $\mu\text{m}$ .
68. The method of Claim 55 wherein the delivery of the substance is by a needle selected from the group consisting of microneedles, catheter needles, and injection needles.
69. The method of Claim 55 wherein said substance is an immunostimulant.
70. The method of claim 55 wherein said substance is an immunosuppressant.
71. The method of claim 55 wherein said substance is selected from the group consisting of an interferon, an interleukin, an anti-inflammatory agent, a tumor targeting compound, and a bacterial cell wall component or synthetic derivative thereof.
72. The method of claim 71 wherein said substance is a lipopolysaccharide or BCG, or a synthetic derivative thereof.
73. The method of Claim 71 wherein the substance is  $\alpha$  interferon.
74. The method of Claim 55 wherein the substance is infused.
75. The method of Claim 55 wherein the substance is delivered as a bolus.
76. The method of Claim 55 further comprising controlling the delivery rate or volume delivered of the substance to the intradermal space.
77. The method of claim 55 wherein said delivery is controlled pursuant to an algorithm having logic components which include physiologic models, rules based models or moving

average methods, therapy pharmacokinetic models, monitoring signal processing algorithms, predictive control models, or combinations thereof.

78. The method of claim 55 wherein the substance is infused at a constant rate.

79. The method of claim 55 wherein the substance is delivered by a combination of infusion and bolus injection.

80. The method of claim 55 wherein the multiple compartments are intradermal and subcutaneous tissue compartments.

81. The method of Claim 55 wherein the access of the one or more compartments is by at least one needle that targets the ID compartment and at least another one needle that targets SC compartment.

82. The method of Claim 55 wherein the delivery to the one or more compartments is by at least one needle which essentially simultaneously targets the ID compartment and SC compartment.

83. The method of Claim 55 wherein the delivery of the one or more compartments is by at least one needle which sequentially targets the ID compartment and SC compartment.

84. The method of Claim 55 wherein the delivery to multiple compartments is by at least one needle that targets the interface of the ID and SC compartments.

85. The method of claim 55 wherein a portion of said therapeutic substance is absorbed more rapidly into the intradermal tissue space, and the remaining portion is absorbed less rapidly into the subcutaneous tissue space.

86. The method of claim 55 wherein the enhanced effectiveness is a decrease in  $T_{\max}$ .

87. The method of claim 55 wherein the enhanced effectiveness is an increase in  $C_{\max}$ .

88. The method of claim 55 wherein the enhanced effectiveness is a decrease in  $T_{\text{lag}}$ .



89. The method of claim 55 wherein the enhanced effectiveness is enhanced absorption rate.

90. The method of claim 55 wherein the enhanced effectiveness is improved bioavailability.